Rec'd PATENT COOPERATION TREATY
31 JUL 1998

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF TRANSMITTAL OF COPIES OF TRANSLATION OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 72.2)

To:

Welckmann
20. JULI 1998
Frist:
Patentanwälte

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ALLEMAGNE

Date of mailing (day/month/year) 13 July 1998 (13.07.98)	
Applicant's or agent's file reference 13060P WO	IMPORTANT NOTIFICATION
International application No. PCT/EP97/00432	**International filing date** (day/month/year) 31 January 1997 (31.01.97)
Applicant LUBITZ, Werner et al	

1. Transmittal of the translation to the applicant.

The International Bureau transmits herewith a copy of the English translation made by the International Bureau of the international preliminary examination report established by the International Preliminary Examining Authority.

2. Transmittal of the copy of the translation to the elected Offices.

The International Bureau notifies the applicant that copies of that translation have been transmitted to the following elected Offices requiring such translation:

BR,CA,CN,GB,JP,KP,KR,NZ,PL,US

The following elected Offices, having waived the requirement for such a transmittal at this time, will receive copies of that translation from the International Bureau only upon their request:

AP,EA,EP,AL,AM,AT,AU,AZ,BA,BB,BG,BY,CH,CU,CZ,DE,DK,EE,FI,GE,HU,IL,IS,KE,KG,KZ,LC, LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,PT,RO,RU,SD,SE,SG,SI,SK,TJ,TM,TR,TT,UA,UG, UZ,VN,OA

3. Reminder regarding translation into (one of) the official language(s) of the elected Office(s).

The applicant is reminded that, where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report.

It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned (Rule 74.1). See Volume II of the PCT Applicant's Guide for further details.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

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Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 13060P WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP97/00432	International filing date (*day/month/year*) 31 January 1997 (31.01.1997)	Priority date (*day/month/year*) 01 February 1996 (01.02.1996)
International Patent Classification (IPC) or national classification and IPC C12N 15/31, 15/70, 15/62, C07K 14/32, C12N 1/21, A61K 39/07		
Applicant LUBITZ, Werner		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25 August 1997 (25.08.1997)	12 May 1998 (12.05.1998)
Name and mailing address of the IPEA/EP European Patent Office D-80298 Munich, Germany Facsimile No. 49-89-2399-4465	Authorized officer Telephone No. 49-89-2399-0

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP97/00432

I. Basis of the report

1. This report has been drawn on the basis of (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

☐ the international application as originally filed.

☒ the description, pages 1 - 47, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____.

☒ the claims, Nos. 1 - 45, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. _____, filed with the letter of _____,
Nos. _____, filed with the letter of _____.

☒ the drawings, sheets/fig 1/3 - 3/3, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

-see sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. _____ .

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.

3...

The S-layer protein (sbsA) of *B. stearothermophilus*, as well as the corresponding DNA sequence, including the associated signal sequence, are known from document D1 (DE 44 25 527 A).

Consequently, at least the following groups of claims (subject to any objections to novelty) can no longer be considered linked by a common inventive concept:

(a) claims 1-14, which concern the expression of the sbsA in a gram-negative organism;
(b) claims 15-20, which concern the sbsA-coding nucleic acid, and the associated vectors and cells;
(c) claims 21-24, which concern the sbsA itself;
(d) claims 25-27, which concern various uses of the sbsA (and thus lack unity in themselves);
(e) claims 28-36, which concern (after preliminary examination) a still unknown sbsB, as well as the associated nucleic acid, cells, uses, etc;
(f) claims 37-45, which concern a (general) process for producing recombinant S-layer protein. Claims 38-45 could possibly also be allocated to other of the above-mentioned groups, depending on the features which distinguish them.

In response to a request from the Examining Authority, the applicants have paid three additional examination

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.

fees and argued that claims 15-27 should be allocated to a common group of inventions.

Although, in principle, for the following reasons, the objection for lack of unity is also upheld as regards claims 15-27, all the claims have been examined, in so far as possible, and reference made to the following groups:

(a) claims 1-14

(b) claims 15-27

(c) claims 28-36

(d) claims 37-45.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-14, 15-27, 28-36, 39	YES
	Claims	37, 38, 40-45	NO
Inventive step (IS)	Claims	1-14	YES
	Claims	15-27, 28-36, 39	NO
Industrial applicability (IA)	Claims	1-45	YES
	Claims		NO

2. Citations and explanations

Novelty and inventive step

1. Group (a)

The production of S-layer proteins from gram-positive bacteria by expression of the corresponding DNA in gram-negative bacteria seems to be still unattained in the prior art published before the priority date. D1 (Gene, 145(1994), pages 115-120) refers expressly thereto.

Novelty and inventive step can thus be acknowledged (see Box VIII, however) for the process as per claim 1 (and accordingly for its dependent claims 2-14).

2. Group (b)

The alleged difference (and the feature which is allegedly essential to the invention and common to this group) from the prior art resides in the fact that "a peptide or polypeptide coding sequence is inserted" into the nucleic acid of SEQ ID No. 1.

As regards inventive step, D2 (WO-A-95/19371) can be considered the closest prior art.

D2 describes fusion proteins of an S-layer protein from *Bacillus sphaericus*, the foreign fusion fraction being located at the N- or C-terminal end of the S-protein.

Strictly speaking, D2 even describes "insertions", as the foreign fraction can be located between the bacillus signal peptide and the remaining S-layer protein fraction (see for example claims 12-16 in D2).

The only difference from D2 would thus be the use of an S-layer protein from another bacillus strain.

However, in view of the generalisation contained in claim 15 (see iii), even the novelty of this claim appears doubtful.

However, even if the above considerations are disregarded, no inventive step can be recognised in an S-layer protein which contains an insertion of totally **undefined** length and **undefined** function at an **undefined** site, in view of the fusion proteins described in D2.

Therefore, at the most, an insertion in a defined position (see for example claim 16) could be considered inventive, provided that the function or purpose of the insertion was additionally defined.

However, even as regards claim 16, the question is raised whether the insertion at different positions can establish a common inventive concept.

The same objections apply to the other claims of this group, i.e. claims 17-27. At best, an inventive step can be established only by reference to claim 16 (with the exception of claims which contain features for which an inventive step can be recognised in other groups; see, for example, claim 19).

3. Group (c)

Contrary to the information in form 405, after an extensive examination of the search report citations, it must be stated that at least claim 33, i.e. the protein coded by the sbsB-gene, is not novel.

Indeed, D3 (J. of Bacteriol., Vol. 176, No. 23 (1994) pages 7182-7189) describes the existence of several S-layer proteins from bacillus (cf. also page 11, lines 2-16 of the present application).

These proteins were isolated with a degree of purity which enabled the N-terminals to be determined (see page 7186 of D3).

The protein itself can thus no longer be considered novel.

In addition, only standard techniques are required to clone a highly purified protein whose N-terminal sequence has been determined.

Therefore, no inventive step can be recognised in the other general claims of this group.

4. Group (d)

The claims of group (d) relate generally to the expression of S-layer proteins from any organism in any host cell.

These claims are for the most part not novel over the teaching of D1 and D2 (see, for example, claims 37, 38, 42-45).

Claims 40 and 41 are not novel either over, for example, D2, as during the expression of an S-layer protein in a host organism the host's S-layer protein is also produced.

Finally, claim 39 is not considered inventive for the reasons given in Section 3.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

As mentioned in Box V, Section 1, no inventive step can be recognised in the process as per claim 1. In view of the prior art (see in particular D1), however, the question is raised why expression in *E. coli* was **not** possible here. The answer could be that the features which enable this expression to occur are absent from the process described in claim 1, in contrast to the prior art.

In Box V, Section 2, claim 15 is acknowledged as involving an inventive step.

From another point of view, however, the conclusion could also be reached that this claim does not even clearly differ from cloned genes.

If it is considered that the "base nucleotide sequence" is "softened" in particular by feature (c), and that, as already mentioned, neither the length, type nor position of the inserted sequence are indicated, the question arises how a delimitation over the (or a) cloned gene can be achieved with such a definition.

As already mentioned, a meaningful assessment of inventive step would be possible only if the position **and** the purpose of the insertion were indicated.

VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS

Absender: MIT DER INTERNATIONALEN VORLÄUFIGEN PRÜFUNG BEAUFTRAGTE BEHÖRDE

Welckmann
E 4. JUNI 1998
Frist:
Patentanwälte

An:

28 Rec'd PCT/PTO 31 JUL 1998 PCT

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Kopernikusstrasse 9
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ALLEMAGNE

MITTEILUNG ÜBER DIE ÜBERSENDUNG DES INTERNATIONALEN VORLÄUFIGEN PRÜFUNGSBERICHTS
(Regel 71.1 PCT)

Absendedatum *(Tag/Monat/Jahr)*	03. 06. 98

Aktenzeichen des Anmelders oder Anwalts	WICHTIGE MITTEILUNG
13060P WO	

Internationales Aktenzeichen	Internationales Anmeldedatum *(Tag/Monat/Jahr)*	Prioritätsdatum *(Tag/Monat/Jahr)*
PCT/EP97/00432	31/01/1997	01/02/1996

Anmelder
LUBITZ, Werner et al.

N.B. DER PRÜFUNGSBERICHT VOM 12.05.98 GILT HIERMIT ALS AUFGEHOBEN

1. Dem Anmelder wird mitgeteilt, daß ihm die mit der internationalen vorläufigen Prüfung beauftragte Behörde hiermit den zu der internationalen Anmeldung erstellten internationalen vorläufigen Prüfungsbericht, gegebenenfalls mit den dazugehörigen Anlagen, übermittelt.

2. Eine Kopie des Berichts wird - gegebenenfalls mit den dazugehörigen Anlagen - dem Internationalen Büro zur Weiterleitung an alle ausgewählten Ämter übermittelt.

3. Auf Wunsch eines ausgewählten Amts wird das Internationale Büro eine Übersetzung des Berichts (jedoch nicht der Anlagen) ins Englische anfertigen und diesem Amt übermitteln.

4. **ERINNERUNG**

Zum Eintritt in die nationale Phase hat der Anmelder vor jedem ausgewählten Amt innerhalb von 30 Monaten ab dem Prioritätsdatum (oder in manchen Ämtern noch später) bestimmte Handlungen (Einreichung von Übersetzungen und Entrichtung nationaler Gebühren) vorzunehmen (Artikel 39 (1)) (siehe auch die durch das Internationale Büro im Formblatt PCT/IB/301 übermittelte Information).

Ist einem ausgewählten Amt eine Übersetzung der internationalen Anmeldung zu übermitteln, so muß diese Übersetzung auch Übersetzungen aller Anlagen zum internationalen vorläufigen Prüfungsbericht enthalten. Es ist Aufgabe des Anmelders, solche Übersetzungen anzufertigen und den betroffenen ausgewählten Ämtern direkt zuzuleiten.

Weitere Einzelheiten zu den maßgebenden Fristen und Erfordernissen der ausgewählten Ämter sind Band II des PCT-Leitfadens für Anmelder zu entnehmen.

Name und Postanschrift der mit der internationalen Prüfung beauftragten Behörde	Bevollmächtigter Bediensteter
Europäisches Patentamt D-80298 München Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Cedex Gestrl Tel. (+49-89) 2399-8064

Formblatt PCT/IPEA/416 (Juli 1992)

VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS

PCT

INTERNATIONALER VORLÄUFIGER PRÜFUNGSBERICHT

(Artikel 36 und Regel 70 PCT)

Aktenzeichen des Anmelders oder Anwalts	**WEITERES VORGEHEN**	siehe Mitteilung über die Übersendung des internationalen vorläufigen Prüfungsberichts (Formblatt PCT/IPEA/416)
13060P WO		
Internationales Aktenzeichen	Internationales Anmeldedatum *(Tag/Monat/Jahr)*	Priority date *(Tag/Monat/Jahr)*
PCT/EP97/00432	31/01/1997	01/02/1996
Internationale Patentklassifikation (IPK) oder nationale Klassifikation und IPK		
C12N15/31		
Anmelder		
LUBITZ, Werner et al.		

1. Dieser Internationale vorläufige Prüfungsbericht wurde von der mit der internationalen vorläufigen Prüfung beauftragten Behörde erstellt und wird dem Anmelder gemäß Artikel 36 übermittelt.

2. Dieser BERICHT umfaßt insgesamt 8 Blätter einschließlich dieses Deckblatts.

   ☐ Außerdem liegen dem Bericht ANLAGEN bei; dabei handelt es sich um Blätter mit Beschreibungen, Ansprüchen und/oder Zeichnungen, die geändert wurden und diesem Bericht zugrunde liegen, und/oder Blätter mit vor dieser Behörde vorgenommenen Berichtigungen (siehe Regel 70.16 und Abschnitt 607 der Verwaltungsrichtlinien zum PCT).

   Diese Anlagen umfassen insgesamt Blätter.

3. Dieser Bericht enthält Angaben zu folgenden Punkten:

I	☒	Grundlage des Berichts
II	☐	Priorität
III	☐	Keine Erstellung eines Gutachtens über Neuheit, erfinderische Tätigkeit und gewerbliche Anwendbarkeit
IV	☒	Mangelnde Einheitlichkeit der Erfindung
V	☒	Begründete Feststellung nach Artikel 35(2) hinsichtlich der Neuheit, der erfinderischen Tätigkeit und der gewerblichen Anwendbarkeit; Unterlagen und Erklärungen zur Stützung dieser Feststellung
VI	☐	Bestimmte angeführte Unterlagen
VII	☐	Bestimmte Mängel der internationalen Anmeldung
VIII	☒	Bestimmte Bemerkungen zur internationalen Anmeldung

Datum der Einreichung des Antrags	Datum der Fertigstellung dieses Berichts
25/08/1997	
Name und Postanschrift der mit der internationalen vorläufigen Prüfung beauftragten Behörde	Bevollmächtigter Bediensteter
Europäisches Patentamt D-80298 München Tel. (+49-89) 2399-0. Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Grosskopf, R Telefon (+49-89) 2399-8714

INTERNATIONALER VORLÄUFIGER PRÜFUNGSBERICHT

Internationales Aktenzeichen PCT/EP97/00432

I. Grundlage des Berichts

1. Dieser Bericht wurde erstellt auf der Grundlage (*Ersatzblätter, die dem Anmeldeamt auf eine Aufforderung nach Artikel 14 hin vorgelegt wurden, gelten im Rahmen dieses Berichts als "ursprünglich eingereicht" und sind ihm nicht beigefügt, weil sie keine Änderungen enthalten.*):

Beschreibung, Seiten:

1-47 ursprüngliche Fassung

Patentansprüche, Nr.:

1-45 ursprüngliche Fassung

Zeichnungen, Blätter:

1/3-3/3 ursprüngliche Fassung

2. Aufgrund der Änderungen sind folgende Unterlagen fortgefallen:

   ☐ Beschreibung, Seiten:
   ☐ Ansprüche, Nr.:
   ☐ Zeichnungen, Blatt:

3. ☐ Dieser Bericht ist ohne Berücksichtigung (von einigen) der Änderungen erstellt worden, da diese aus den angegebenen Gründen nach Auffassung der Behörde über den Offenbarungsgehalt in der ursprünglich eingereichten Fassung hinausgehen (Regel 70.2(c)):

4. Etwaige zusätzliche Bemerkungen:

IV. Mangelnde Einheitlichkeit der Erfindung

1. Auf die Aufforderung zur Einschränkung der Ansprüche oder zur Zahlung zusätzlicher Gebühren hat der Anmelder:

   ☐ die Ansprüche eingeschränkt.

   ☒ zusätzliche Gebühren entrichtet.

   ☐ zusätzliche Gebühren unter Widerspruch entrichtet.

   ☐ weder die Ansprüche eingeschränkt noch zusätzliche Gebühren entrichtet.

2. ☐ Die Behörde hat festgestellt, daß das Erfordernis der Einheitlichkeit der Erfindung nicht erfüllt ist, und hat gemäß Regel 68.1 beschlossen, den Anmelder nicht zur Einschränkung der Ansprüche oder zur Zahlung zusätzlicher Gebühren aufzufordern.

3. Die Behörde ist der Auffassung, daß das Erfordernis der Einheitlichkeit der Erfindung nach den Regeln 13.1, 13.2 und 13.3

   ☐ erfüllt ist

   ☒ aus folgenden Gründen nicht erfüllt ist:

   siehe Beiblatt

4. Daher wurde zur Erstellung dieses Berichts eine internationale vorläufige Prüfung für folgende Teile der internationalen Anmeldung durchgeführt:

   ☒ alle Teile.

   ☐ die Teile, die sich auf die Ansprüche Nr. beziehen.

V. Begründete Feststellung nach Artikel 35(2) hinsichtlich der Neuheit, der erfinderischen Tätigkeit und der gewerblichen Anwendbarkeit; Unterlagen und Erklärungen zur Stützung dieser Feststellung

1. Feststellung

Neuheit (N)	Ja:	Ansprüche	1-14, 15-27, 28-36, 39
	Nein:	Ansprüche	37, 38, 40-45
Erfinderische Tätigkeit (ET)	Ja:	Ansprüche	1-14
	Nein:	Ansprüche	15-27, 28-36, 39
Gewerbliche Anwendbarkeit (GA)	Ja:	Ansprüche	1-45
	Nein:	Ansprüche	

2. Unterlagen und Erklärungen

   siehe Beiblatt

VIII. Bestimmte Bemerkungen zur internationalen Anmeldung

Zur Klarheit der Patentansprüche, der Beschreibung und der Zeichnungen oder zu der Frage, ob die Ansprüche in vollem Umfang durch die Beschreibung gestützt werden, ist folgendes zu bemerken:

siehe Beiblatt

1. **Ad item IV:**

Das S-Layer-Protein (sbsA) aus B. stearothermophilus, sowie die entsprechende DNA-Sequenz inklusive der dazugehörigen Signalsequenz ist aus Dokument D1 (DE 4425527) bekannt.
Daher können mindestens die folgenden Gruppen von Ansprüchen (vorbehaltlich eventueller Neuheitseinwände) nicht mehr als durch ein gemeinsames erfinderisches Konzept verbunden angesehen werden:

(a) Ansprüche 1-14, die sich auf die Expression des sbsA in einem gram-negativen Organismus beziehen
(b) Ansprüche 15-20, die sich auf die Nukleinsäure beziehen, die für sbsA kodiert sowie die dazugehörigen Vektoren und Zellen
(c) Ansprüche 21-24, die sich auf das sbsA selbst beziehen
(d) Ansprüche 25-27, die sich auf verschiedene Verwendungen des sbsA beziehen (und somit in sich uneinheitlich sind)
(e) Ansprüche 28-36, die sich auf (nach vorläufiger Prüfung) ein noch nicht bekanntes sbsB beziehen, sowie die dazugehörigen Nukleinsäure, Zellen, Verwendungen etc.
(f) Anspruch 37-45, die sich auf ein (generelles) Verfahren zur Herstellung von rekombinantem S-Laser-Protein beziehen. Die Ansprüche 38-45 können evtl. auch anderen der oben genannten Gruppen zugeordnet werden, in Abhängigkeit der sie spezifizierende Merkmale.

Die Anmelderin hat, in Erwiderung auf die Aufforderung seitens der beauftragten Behörde drei weitere Prüfungsgebühren bezahlt und argumentiert, die Ansprüche 15-27 seien einer gemeinsamen Erfindungsgruppe zuzuordnen.
Obwohl aus den unten genannten Gründen, im Prinzip die Einheitlichkeitseinwände auch für die Ansprüche 15-27 aufrecht erhalten werden, werden dennoch, soweit möglich, alle Ansprüche geprüft, wobei dabei auf die folgenden Gruppen Bezug genommen wird:

(a) Ansprüche 1-14
(b) Ansprüche 15-27
(c) Ansprüche 28-36

(d) Ansprüche 37-45

2. **Zu Punkt V: Neuheit und erfinderische Tätigkeit**

2.1 Gruppe (a)

Die Herstellung von S-Layer-Proteinen aus gram-positiven Bakterien durch Expression der entsprechenden DNA in gram-negativen Bakterien scheint im Stand der Technik, der vor dem Prioritätstag veröffentlicht wurde, noch nicht gelungen zu sein. Darauf wird ausdrücklich in D1 (Gene, 145 (1994), Seiten 115-120) verwiesen.
Somit kann für das Verfahren gemäß Anspruch 1 (und entsprechend für die abhängigen Ansprüche 2-14) Neuheit und erfinderische Tätigkeit anerkannt werden (siehe allerdings Punkt VIII).

2.2 Gruppe (b)

Der angebliche Unterschied (und das angeblich erfindungswesentliche und gemeinsame Merkmal innerhalb dieser Gruppe) zum Stand der Technik liegt in der Tatsache, daß in die Nukleinsäure gemäß SEQ ID NO.1 "eine für ein Peptid oder Polypeptid kodierende Sequenz inseriert ist".
Im Hinblick auf die erfinderische Tätigkeit kann D2 (WO 95/19371) als der nächstliegende Stand der Technik angesehen werden.
D2 beschreibt Fusionproteine eines S-Layer-Proteins aus Bacillus sphaericus, wobei sich der Fremdfusionsanteil entweder am N- oder am C-terminalen Ende des S-Proteins befinden kann.
Streng genommen beschreibt D2 sogar "Insertionen", da sich der Fremdanteil zwischen dem Signalpeptid aus Bacillus und dem übrigen S-Layer-Proteinanteil befinden kann (siehe z.B. Ansprüche 12-16 in D2).
Somit wäre der einzige Unterschied zu D2 die Verwendung eines S-Layer-Proteins aus einem anderen Bacillus-Stamm.
Allerdings scheint auf Grund der in Anspruch 15 enthaltenen Verbreiterung (siehe iii) sogar die Neuheit dieses Anspruchs in Frage gestellt zu sein.

Aber selbst wenn man die eben genannten Erwägungen außer acht läßt, kann

einem S-Layer-Protein welches eine Insertion von völlig **undefinierter** Länge und **undefinierter** Funktion an einem **undefinierten** Ort enthält, im Hinblick auf die in D2 beschriebenen Fusionsproteine keine erfinderische Tätigkeit zuerkannt werden.
Als erfinderisch könnte daher allenfalls eine Insertion in einer definierten Postion angesehen werden (siehe z.B. Anspruch 16), wobei allerdings zusätzlich noch die Funktion oder der Zweck der Insertion definiert werden sollte.
Aber selbst im Hinblick auf Anspruch 16 stellt sich die Frage ob die Insertion an verschiedenen Positionen ein gemeinsames erfinderisches Konzept etablieren kann.
Für die anderen Ansprüche dieser Gruppe d.h. Ansprüche 17- 27, gelten die selben Einwände, d.h. eine erfinderische Tätigkeit kann allenfalls durch Bezug auf Anspruch 16 hergestellt werden (mit Ausnahme von Ansprüchen, die Merkmale enthalten für die in anderen Gruppen eine erfinderische Tätigkeit anerkannt werden kann, sieh z.B. Anspruch 19).

2.3 Gruppe (c)

Im Gegensatz zu der Aussage im Formblatt 405 muß nach eingehender Prüfung der im Recherchenbericht zitierten Dokumente, festgestellt werden, daß zumindest Anspruch 33, d.h. das durch das sbsB-Gen kodierte Protein nicht neu ist.
Tatsächlich beschreibt D3 (J. of Bacteriol. Vol. 176, No. 23 (1994) Seiten 7182-7189) die Existenz mehrerer S-Layer-Proteine aus Bacillus (vgl. auch Seite 11, Zeilen 2-16 der vorligenden Anmeldung).
Diese wurden in einer Reinheit isoliert, die die Bestimmung der N-Termini erlaubte (siehe Seite 7186 in D3).
Somit kann das Protein selbst nicht mehr als neu angesehen werden.
Darüber hinaus bedarf die Klonierung eines Proteins, das hochgereinigt wurde und dessen N-terminale Sequenz bestimmt worden ist ausschließlich der Verwendung von Standardtechniken.
Somit kann den anderen allgemeinen Ansprüchen dieser Gruppe keine erfinderische Tätigkeit zuerkannt werden.

2.4 Gruppe (d)

Die Ansprüche der Gruppe (d) richten sich in allgemeiner Form auf die Expression von S-Layer-Proteinen aus jedem beliebigen Organismus in jeder beliebigen Wirtszelle, wobei die S-Layer-Proteine durch eine "Insertion" gekennzeichnet sind. Für diese Ansprüche gelten primär die bereits unter Punkt 2.2 erwähnten Einwände mangelnder erfinderischer Tätigkeit, zumindest für die Ansprüche im derzeitigen Wortlaut.
In dieser Gruppe kommt allerdings dazu, daß zumindest in Anspruch 37, nicht einmal die zu modifizierende Sequenz angegeben ist und in keinem der weiteren Ansprüche eine spezifische Position zur Insertion angegeben ist.
Somit kann ein Fachmann bei fehlender Angabe des Referenz S-Layer-Proteins, nicht bestimmren, ob eine Nukleinsäure für ein S-Layer-Protein mit oder ohne Insertion kodiert.
Darüber hinaus ist der angebliche erfinderische Effekt, nämlich die Erhaltung der S-Layer-Struktur, für die große Zahl der existierenden unterschiedlichen S-Layer-Proteinen völlig spekulativ.
Auch die Ansprüche 40 und 41 sind nicht erfinderisch im Hinblick auf z.B. D2, da bei der Expression eines S-Layer-Proteins in einem Wirtsorganismus auch das wirtseigene S-Layer-Protein gebildet wird.
Schließlich ist Anspruch 39 aus den unter 2.3 genannten Gründen als nicht erfinderisch anzusehen.

3. **Zu Punkt VIII:**

Wie unter 2.1 erwähnt kann dem Verfahren gemäß Anspruch 1 eine erfinderische Tätigkeit zuerkannt werden. Im Hinblick auf den Stand der Technik (siehe insbes. D1) stellt sich allerdings die Frage, warum dort die Expression in E. coli **nicht** möglich war. Die Konsequenz könnte sein, daß in dem in Anspruch 1 beschriebenen Verfahren diejenigen Merkmale fehlen, die diese Expression, im Gegensatz zum Stand der Technik, ermöglichen.
So stellt sich z.B. die Frage, ob der in der vorliegenden Anmeldung verwendete E. coli Stamm oder der im Stand der Technik beschriebene Stamm den Regelfall darstellt. Im letzteren Fall, scheint eine Einschränkung auf den in der vorliegenden Anmeldung verwendeten Stamm notwendig zu sein.
Unter Punkt 2.2 wurde dem Anspruch 15 eine erfinderische Tätigkeit abgesprochen.

Bei anderer Betrachtungsweise kann man allerdings auch zu der Auffassung kommen, daß sich dieser Anspruch nicht einmal eindeutig von klonierten Genen unterscheidet.
Zieht man zum einen heran, daß die "Basisnukleotidsequenz" insbesondere durch das Merkmal (c) "aufgeweicht" ist und zum anderen, wie erwähnt, weder die Länge noch die Art noch die Position der inserierten Sequenz angegeben ist, so stellt sich die Frage wie mit solch einer Definition eine Abgrenzung von dem (oder einem) klonierten Gen erzielt werden soll.
Wie bereits oben erwähnt, erscheint eine sinnvolle Prüfung einer erfinderischen Tätigkeit allenfalls dann möglich, wenn Position **und** Zweck der Insertion angegeben werden.

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF TRANSMITTAL OF COPIES OF TRANSLATION OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 72.2)

From the INTERNATIONAL BUREAU

To:

WEICKMANN, H.
Kopernikusstrasse 9
D-81679 München
ALLEMAGNE

Date of mailing (day/month/year) 21 August 1998 (21.08.98)	
Applicant's or agent's file reference 13060P WO	**IMPORTANT NOTIFICATION**
International application No. PCT/EP97/00432	**International filing date (day/month/year)** 31 January 1997 (31.01.97)
Applicant LUBITZ, Werner et al	

1. Transmittal of the translation to the applicant.

The International Bureau transmits herewith a copy of the English translation made by the International Bureau of the international preliminary examination report established by the International Preliminary Examining Authority.

2. Transmittal of the copy of the translation to the elected Offices.

The International Bureau notifies the applicant that copies of that translation have been transmitted to the following elected Offices requiring such translation:

BR,CA,CN,GB,JP,KP,KR,NZ,PL,US

The following elected Offices, having waived the requirement for such a transmittal at this time, will receive copies of that translation from the International Bureau only upon their request:

AP,EA,EP,AL,AM,AT,AU,AZ,BA,BB,BG,BY,CH,CU,CZ,DE,DK,EE,FI,GE,HU,IL,IS,KE,KG,KZ,LC, LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,PT,RO,RU,SD,SE,SG,SI,SK,TJ,TM,TR,TT,UA,UG, UZ,VN,OA

3. Reminder regarding translation into (one of) the official language(s) of the elected Office(s).

The applicant is reminded that, where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report.

It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned (Rule 74.1). See Volume II of the PCT Applicant's Guide for further details.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Diana Nissen

Telephone No. (41-22) 338.83.38

Translation

11

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 13060P WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP97/00432	International filing date (*day/month/year*) 31 January 1997 (31.01.1997)	Priority date (*day/month/year*) 01 February 1996 (01.02.1996)
International Patent Classification (IPC) or national classification and IPC C12N 15/31, 15/70, 15/62, C07K 14/32, C12N 1/21, A61K 39/07		
Applicant LUBITZ, Werner		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8. sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

CORRECTED VERSION

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25 August 1997 (25.08.1997)	03 June 1998 (03.06.1998)
Name and mailing address of the IPEA/EP European Patent Office D-80298 Munich, Germany Facsimile No. 49-89-2399-4465	Authorized officer Telephone No. 49-89-2399-0

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP97/00432

I. Basis of the report

1. This report has been drawn on the basis of (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

☐ the international application as originally filed.

☒ the description, pages 1-47, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____.

☒ the claims, Nos. 1-45, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. _____, filed with the letter of _____,
Nos. _____, filed with the letter of _____.

☒ the drawings, sheets/fig 1/3-3/3, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 6g.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

see supplemental sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. _____

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.3.

1. The S-layer protein (sbsA) from B. stearothermophilus and the corresponding DNA sequence including the relevant signal sequence is known from document D1 (DE-A-4 425 527).

Consequently, at least the following groups of claims (subject to possible objections to novelty) can no longer be considered to be linked by a common inventive concept:

(a) claims 1-14 which refer to the expression of the sbsA in a Gram-negative organism
(b) claims 15-20 which refer to the nucleic acid which codes for sbsA and the corresponding vectors and cells
(c) claims 21-24 which refer to the sbsA itself
(d) claims 25-27 which refer to various uses of the sbsA (and are therefore lacking in unity per se)
(e) claims 28-36 which (after preliminary examination) refer to a yet unknown sbsB and to the corresponding nucleic acid, cells, uses, etc.
(f) claims 37-45 which refer to a (general) process for producing recombinant S-laser protein. Claims 38-45 may possibly also be associated with others of the aforementioned groups, depending on the features which specify them.

In reply to the demand made by the Examining Authority, the applicant paid three further examination fees and argues that claims 15-27 are associated with one common group of inventions. Although for reasons which follow, the objection to unity of invention is maintained in principle for

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV. 3.

claims 15-27, as far as possible all the claims were examined, reference being made to the following groups:

(a) claims 1-14
(b) claims 15-27
(c) claims 28-36
(d) claims 37-45

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-14,15-27,28-36,39	YES
	Claims	37,38,40-45	NO
Inventive step (IS)	Claims	1-14	YES
	Claims	15-27,28-36,39	NO
Industrial applicability (IA)	Claims	1-45	YES
	Claims		NO

2. Citations and explanations

2.1 Group (a)

Producing S-layer proteins from Gram-positive bacteria by expressing the corresponding DNA in Gram-negative bacteria does not yet appear to have been successful in the prior art published before the priority date. Particular reference is made to D1 (Gene, 145 (1994), pages 115-120). Consequently, novelty and inventive step can be recognised for the process as per claim 1 (and accordingly for dependent claims 2-14) (see, however, Box VIII).

2.2 Group (b)

The supposed difference (and the supposed common feature within this group which is essential to the invention) over the prior art lies in the fact that "a sequence coding for a peptide or a polypeptide is inserted" in the nucleic acid as per SEQ ID NO. 1.

D2 (WO-A-95/19371) can be considered to be the closest prior art with regard to inventive step.

D2 discloses fusion proteins of an S-layer protein

from Bacillus sphaericus, the foreign fusion part being located either on the N or C terminal end of the S-protein.

Strictly speaking, D2 actually discloses "insertions", since the foreign part may be located between the signal peptide from Bacillus and the remaining S-layer protein part (see, for example, claims 12-16 in D2).

Thus, the only difference in relation to D2 would be the use of an S-layer protein from another Bacillus strain.

However, the extension contained in claim 15 (see iii) appears to throw even the novelty of this claim into question.

Nevertheless, even if the aforementioned considerations are disregarded, in view of the fusion proteins described in D2 no inventive step can be recognised for an S-layer protein containing an insertion of completely **undefined** length and **undefined** function at an **undefined** place.

Consequently, at best an insertion in a defined position could be regarded as inventive (see, for example, claim 16), but the function or the purpose of the insertion would also have to be defined.

However, even in view of claim 16, the question arises of whether the insertion at different positions can establish a common inventive concept.

The same objections, that is that an inventive step can at best be established by referring to claim 16

(with the exception of claims containing features for which an inventive step can be recognised in other groups, see, for example, claim 19) apply to the other claims of this group, that is claims 17-27.

2.3 Group (c)

In contrast to the statement made in form 405, it must be noted after thorough examination of the search report citations that at least claim 33, that is the protein coded by the sbsB gene, is not novel.

Actually, D3 discloses (J. of Bacteriol. vol. 176, no. 23 (1994), pages 7182-7189) the existence of several S-layer proteins from Bacillus (see also page 11, lines 2-16 of the present application). These were isolated in a purity which enables the N-terminals to be determined (see page 7186 in D3). Thus, the protein itself can no longer be considered novel.
Moreover, cloning a protein which was ultrapurified and whose N-terminal sequence was determined merely requires the use of standard techniques.

Consequently, no inventive step can be recognised for the other general claims of this group.

2.4 Group (d)

The claims of group (d) relate generally to the expression of S-layer proteins from any desired organism in any desired host cell, the S-layer proteins being characterised by an "insertion". The objections concerning a lack of inventive step already mentioned in point 2.2 primarily apply to these claims, at least as currently worded.

However, in this group, at least in claim 37, the sequence to be modified is not indicated once and a specific insertion position is not indicated in any of the other claims.
Consequently, owing to the lack of information concerning the S-layer protein reference, a person skilled in the art cannot determine whether a nucleic acid codes for an S-layer protein with or without insertion.
Moreover, the supposed inventive effect, namely the maintaining of the S-layer structure, is completely speculative for the large number of different S-layer proteins that exist.

Nor are claims 40 and 41 inventive in view of, for example, D2, since when an S-layer protein is expressed in a host cell, the host S-layer protein is also formed.

Finally, for the reasons indicated in 2.3, claim 39 is not considered to be inventive.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

3. As mentioned in 2.1, an inventive step can be recognised for the process as per claim 1. In view of the prior art (see in particular D1), the question arises, however, of why expression in E.coli was **not** possible. The reason could be that, unlike in the prior art, those features which enable this expression are missing from the process described in claim 1.

Thus, for example, the question arises of whether the E.coli strain used in the present application or the strain described in the prior art represents the rule. In the latter case, it appears necessary to limit the subject to the strain used in the present application.

An inventive step is not acknowledged for claim 15 under point 2.2.

If looked at in a different light, however, one may also come to the conclusion that this claim does not once differ clearly from cloned genes.

Given that the "basis nucleotide sequence" is "weakened" in particular by feature (c) and that, as already mentioned, neither the length, nor the type, nor the position of the inserted sequence is indicated, the question arises of how a delimitation over the (or a) cloned gene is to be achieved with such a definition.

As already mentioned above, a meaningful examination of inventive step appears to be possible at best if

VIII. Certain observations on the international application

the position and purpose of the insertion are indicated.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/00432

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/31 C12N15/70 C12N15/62 C07K14/32 C12N1/21
A61K39/07

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C12N C12P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 19371 A (SOLVAY ;DEBLAERE ROLF Y (BE); OESOMER JAN (BE); DHAESE PATRICK (BE) 20 July 1995	37,40-44
A	see the whole document	1-36

X	OE 44 25 527 A (VOGELBUSCH GMBH) 25 January 1996 cited in the application	15,17, 18, 20-38, 43-45
Y	see the whole document	1,2,4-6, 13,14,19

	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 June 1997	01.07.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Kania, T

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CANADIAN JOURNAL OF MICROBIOLOGY, vol. 40, no. 9, September 1994, pages 777-782, XP000674689 8INGLE W. AND SMIT J.: "Alkaline phosphatase and a cellulase reporter protein are not exported from the cytoplasm when fused to large N-terminal portions of the Caulobacter crescentus surface (S)-layer protein" cited in the application see the whole document	1,2,4-6, 13,14,19
A	MOLECULAR MICRO8IOLOGY, vol. 9, no. 1, 1993, pages 97-109, XP000674434 PEYRET J. ET AL.: "Characterization of the csp8 gene encoding PS2, an ordered surface-layer protein in Corynebacterium glutamicum" cited in the application * siehe das ganze Dokument, bes. S.98 letzter Absatz bis S.99 *	1,2,4,5
A	WO 91 13155 A (8OEHRINGER MANNHEIM GMBH) 5 September 1991 see the whole document	26
A	GENE, vol. 145, no. 1, 1994, pages 115-120, XP002032765 KUEN 8. ET AL.: "Sequence analysis of the sbsA gene encoding the 130-kDa surface-layer protein of bacillus stearothermophilus strain PV72" cited in the application see the whole document	1-27,37, 38,40-45
A	JOURNAL OF 8ACTERIOLOGY, vol. 176, no. 23, December 1994, pages 7182-7189, XP000674692 SARA M. AND SLEYTR U.: "Comparative studies of S-layer proteins from 8acillus stearothermophilus strains expressed during growth in continuous culture under oxygen-limited and non-oxygen-limited conditions" cited in the application see the whole document	28-37, 39-45

-/--

3

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	MOLECULAR MICROBIOLOGY, vol. 19, no. 3, February 1996, pages 495-503, XP000675407 KUEN B. ET AL.: "Heterologous expression and self-assembly of the S-layer protein SbsA of Bacillus stearothermophilus in Escherichia coli" see the whole document	1-3,13, 14
T	JOURNAL OF BACTERIOLOGY, vol. 179, no. 5, March 1997, pages 1664-1670, XP000674432 KUEN B. ET AL.: "Molecular characterization of the Bacillus stearothermophilus PV72 S-layer gene sbsB induced by oxidative stress" see the whole document	28-45
T	TIBTECH, vol. 15, no. 1, January 1997, pages 20-26, XP002032144 SLEYTR U. AND SARA M: "Bacterial and archaeal S-layer proteins: structure-function relationships and their biotechnological applications" see the whole document	1-45

INTERNATIONAL SEARCH REPORT

International application No.
PCT/ EP 97/ 00432

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 25, 26, 35
because they relate to subject matter not required to be searched by this Authority, namely:

Observation: although claims 25, 26 and 35 concern a process for treatment of the human or animal body, the search was carried out and based on the cited effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter[illegible]onal Application No
PCT/EP 97/00432

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9519371 A	20-07-95	EP 0738278 A	23-10-96
DE 4425527 A	25-01-96	NONE	
WO 9113155 A	05-09-91	DE 4005874 A	07-11-91
		AU 7237391 A	18-09-91
		DE 59101580 D	09-06-94
		EP 0516655 A	09-12-92
		IE 64613 B	23-08-95
		JP 5503014 T	27-05-93
		US 5470573 A	28-11-95